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CLINICAL INVESTIGATION **Normal Tissues**

CORONARY HEART DISEASE AFTER RADIOTHERAPY FOR PEPTIC ULCER DISEASE

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Purpose: To evaluate the risk of coronary heart disease (CHD) and cerebrovascular disease after radiotherapy (RT) for peptic ulcer disease.

Methods and Materials: Peptic ulcer disease patients treated with RT (n = 1859) or by other means (n = 1860) at the University of Chicago Medical Center between 1936 and 1965, were followed through 1997. The observed numbers of cause-specific deaths were compared with the expected numbers from the general population rates. During RT, 5% of the heart was in the treatment field and the remainder of the heart mostly received scattered radiation. A volume-weighted cardiac dose was computed to describe the average tissue dose to the entire organ. We used Cox proportional hazards regression analysis to analyze the CHD and cerebrovascular disease risk associated with RT, adjusting for confounding factors.

Results: Greater than expected CHD mortality was observed among the irradiated patients. The irradiated patients received volume-weighted cardiac doses ranging from 1.6 to 3.9 Gy and the portion of the heart directly in the field received doses of 7.6–18.4 Gy. The CHD risk increased with the cardiac dose (p trend = 0.01). The cerebrovascular disease risk was not associated with the surrogate carotid dose.

Conclusion: The excess CHD risk in patients undergoing RT for peptic ulcer disease decades previously indicates the need for long-term follow-up for cardiovascular disease after chest RT. © **2005 Elsevier Inc.**

Coronary heart disease, Peptic ulcer disease, Cerebrovascular disease, Radiotherapy, Smoking.

INTRODUCTION

The adverse cardiac effects of high-dose radiotherapy (RT) were first recognized in the late 1960s, when cases of heart disease were observed among patients treated with RT for Hodgkin's lymphoma and other mediastinal tumors (1). Pericardial disease was initially thought to be the predominant radiation-induced heart damage, but additional follow-up of Hodgkin's lymphoma patients showed a statistically significant increased risk of coronary heart disease (CHD) many years after undergoing megavoltage mantle therapy (2, 3) that yielded a total mediastinal dose of 40–44 Gy. An excess risk of myocardial infarction has also been linked to the adjuvant RT for breast cancer used before 1980 (4–7). It has not been clear, however, whether relatively low therapeutic doses from modern RT for Hodgkin's lymphoma (3, 8, 9) or early breast cancer (10–14) have resulted in a statistically significant reduction in the heart disease risk in RT patients.

Recent mortality and morbidity data from studies of the Japanese atomic bomb survivors have demonstrated a statistically significant dose–response relation for mortality from heart disease and stroke at doses of <4–5 Gy (15, 16), suggesting that an excess risk of heart disease can occur after exposure to low-dose RT. The excess risk in the atomic bomb survivors persisted for several decades after the radiation exposure. An excess risk of heart disease after exposure to low doses has also been reported from studies of patients undergoing RT for benign disease (e.g., ankylosing spondylitis [17], metropathia hemorrhagica [18]) and occu-

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pationally exposed radiologists and radiologic technologists in the United States (19–21). No excess heart disease risk was found in studies of fluoroscoped tuberculosis patients (22) or U.K. radiologists (23).

In the 1940–1960s, RT was frequently used to treat patients with peptic ulcer disease (PUD) at the University of Chicago (24, 25). During RT, a small portion (estimated to be about 5%) of the heart volume was in the treatment field and the remaining volume of the heart was mostly exposed to scattered radiation. A cohort comprising irradiated and nonirradiated PUD patients has been studied since 1974, with the latest follow-up mortality data available through 1997. Earlier mortality studies of this cohort focused on cancer (26, 27) and showed greater than expected mortality from diseases of the circulatory system associated with RT, but no dose–response analysis was conducted. In this paper, we discuss the results of a quantitative assessment of the risk of heart disease mortality in relation to the estimated radiation dose, controlling for smoking and other cardiovascular risk factors.

METHODS AND MATERIALS

Study population and follow-up

The characteristics of this population and study design have been previously described (27). In brief, the study cohort comprised 3719 subjects (1859 irradiated and 1860 nonirradiated), retrospectively selected from among about 4000 PUD patients treated at the University of Chicago between 1937 and 1965. Because the principal rationale for RT was to reduce gastric secretions, patients selected for RT tended to have a high acid production The irradiated patients also were hospitalized and had more severe manifestation of PUD than an ulcer-patient population in general (24, 25). No documented information was available to compare the characteristics of the irradiated and nonirradiated patients, but several factors, such as age, gender, ulcer location, complications (e.g., stenosis, hemorrhage, and perforation), were considered in patient selection (25). The nonirradiated patients, who served as the comparison group in this study, were selected from among PUD patients who were treated by medication and/or surgically, and were similar to the irradiated group in terms of gender, age, and ulcer type. The University of Chicago Medical Center Institutional Review Board approved the follow-up procedures, and all patients provided informed consent for data collection.

Follow-up for vital status and cause of death included searches of the National Death Index Plus, Social Security Administration Mortality Files and Presumed Living Files, and Pension Benefit Information records. For irradiated patients, the date of entry into follow-up observation was the date at first treatment; for nonirradiated patients, it was the date of first PUD diagnosis or the date of the first visit to the University of Chicago Hospital, whichever occurred later. The follow-up ended at the date of death, date last known to be alive, or December 31, 1997, whichever occurred earliest. The cause of death recorded on death certificates was coded according to the Eighth Revision of the International Classification of Diseases (ICD-8) (28). We combined "acute myocardial infarction" (ICD-8 code 410), "other acute or subacute forms of ischemic heart disease" (ICD-8 code 411), "chronic ischemic heart disease" (code 412), "angina pectoris" (code 413), and "asymptomatic ischemic heart disease" (code 414) into one category and "coronary heart disease," "hypertensive disease" (codes 400–404) and "other forms of heart disease" (ICD-8 codes 420–429) into another category, "other heart disease." All "cerebrovascular disease" (CVD) deaths (ICD-8 codes 430–438) were grouped together.

Radiation doses

RT for PUD at the University of Chicago, described in detail elsewhere, was highly standardized (24–26). Several machines were used, but, with rare exceptions, these were orthovoltage X-ray machines with 250-kVp X-ray beams and effective energies equivalent to 1.3–1.5 mm Cu half-value layers. Treatments were anterior and posterior parallel-opposed fields (typically 13 cm × 13 cm), centered on the stomach and under fluoroscopic control starting in 1949. RT was delivered in daily fractions of 1.5 Gy at a dose rate of 0.3 Gy/min during one or two 6–14-day treatment courses; the goal, although it varied slightly over the years, was to provide a stomach dose of 16–17 Gy at each course.

A statistically significant dose gradient occurred across the heart, decreasing with increasing distance from the edge of the treatment field. It was estimated by one of us (M.L.G.), who administered many of the treatments, that about 5% of the heart (apex) was directly in the radiation field during all treatments. The remainder of the heart received scattered radiation.

The cardiac doses were estimated using measurements in an adult male Alderson phantom. The machine used to irradiate the phantom was one of the machines (Maxitron 250; General Electric, Milwaukee, WI) used to treat the patients in the study. The beam was defined by the machine collimators with a lead rubber cutout, providing additional shielding of adjacent organs. Thermoluminescent dosimeters were placed on a three-dimensional grid throughout the torso of the phantom. The thermoluminescent dosimeters were standardized relative to a ^{60}Co beam, calibration traceable to the National Institute of Standards and Technology, with measured energy correction factors applied for orthovoltage beams.

We derived a volume-weighted average dose to the entire heart by summing the in-field dose received in the apex of the heart weighted by its proportion of the organ volume (5%) and the average of the dose received in the remainder of the heart weighted by its volume proportion (95%). The doses delivered to the stomach for individual patients were obtained from the RT records. The measurements were renormalized on the basis of the patient's stomach dose to obtain each patient's volume-weighted average dose to the heart. The total average cumulative cardiac dose for each patient was obtained by summing the volume-average cardiac dose over all treatment courses.

For the analysis of stroke, the carotid doses were estimated using the thyroid dose as a proxy.

Statistical analysis

Person-years were computed beginning 1 year after the date of entry into the cohort to exclude subjects who might have died of preexisting medical conditions after PUD treatment. The expected numbers of deaths were estimated by summing the products of age-, gender-, race-, and calendar year-specific person-years of observation times the corresponding mortality rates for the general population of the United States for each cause of interest. The ratio of observed to expected number of deaths (O/E ratio), and its 95% confidence interval (CI), were computed.

Cox proportional hazards regression analysis (29, 30), as imple-

mented in the SAS software package, PHREG procedure (31), was used to assess the relationship with radiation exposure. The hazard function for an individual at time t after study entry, and with covariates $z_1, \ldots, z_k$, was modeled as

$$\lambda(t; z_1, \ldots, z_k) = \lambda_0(t) exp\{\beta_1 z_1 + \ldots + \beta_k z_k\},$$

where $\lambda_0(t)$ is the baseline or background rate (hazard) as a function of time t since entry into the cohort and $exp\{\beta_1 z_1 + \ldots + \beta_k z\}$ is the relative risk (RR) function with unknown parameters $\beta_1, \ldots, \beta_k$. Covariates $z_1, \ldots, z_k$ represented such factors as radiation exposure, radiation dose, and potential confounders. Other adjustments were made by stratification of the model.

Average cardiac doses and proxy carotid doses were categorized into quartiles, and quartile-specific relative risks and 95% CIs were computed. Trend tests were based on continuous variables.

Possible interactions between RT and cigarette smoking were examined using the same overall statistical model but with dichotomous variables for the main effects of RT and smoking and, for interaction, the product of these two variables.

RESULTS

A total of 3719 patients contributed 92,979 person-years, with an average follow-up duration of 22.5 years for irradiated and 27.5 years for nonirradiated patients. By December 31, 1997, 83.6% of the irradiated and 81.1% of the nonirradiated patients had died. In both groups of patients, 2.5% were confirmed alive, and 13.9% of irradiated and 16.5% of nonirradiated patients had been lost to follow-up. Of the 2936 deaths, 2187 were from causes other than cancer, including 1097 from circulatory diseases.

Table 1 shows the effects of the potential confounding factors on the risks of CHD and CVD, and the distributions of these factors among irradiated and nonirradiated patients. The RRs of both CHD and CVD increased with increasing age at the treatment for PUD and were also significantly greater among those treated in earlier calendar years. A statistically significant elevated RR of CHD was found for men, divorced or widowed persons, and current and former smokers. The RRs of CVD in relation to these variables, except for gender, generally followed the same patterns. Because the irradiated and nonirradiated patients were distributed differently with respect to all variables presented, these factors were treated as potential confounders in all statistical analyses. Alcohol consumption was not significantly associated with the risk of either CHD or CVD but was included as another potential confounder because of the protective effect on CHD of moderate alcohol consumption reported in the literature (32).

The O/E ratios showed that all-cause mortality for the irradiated group was increased by 19% compared with the U.S. general population rates (Table 2). In contrast, the nonirradiated group had an 8% deficit of mortality from all causes. We had previously reported that the excess mortality in the irradiated patients was largely attributable to cancer (O/E ratio of 1.65, data not shown), especially of the stomach, pancreas, and lung (27), but the present data showed that it was also due to diseases other than cancer, namely circulatory (O/E ratio 1.10) and digestive (O/E ratio 1.70) diseases. The excess mortality from circulatory disease among the irradiated patients was largely accounted for by a 19% excess of CHD mortality (O/E ratio 1.19), which made up about one-third of mortality from all circulatory diseases. Mortality from gastric and duodenal ulcers accounted for about 40% of mortality from digestive diseases and was increased more than threefold in both irradiated and nonirradiated patients compared with the general population. The latter finding suggested that the excess gastric and duodenal ulcer mortality was most likely related to the condition for which these patients were treated and that the excess CHD mortality might have been specifically related to the use of RT.

The RR of mortality from different causes in Table 2 were based on an internal comparison and showed the risk of disease associated with RT relative to those who did not undergo RT. Within the first 10 years after treatment, no statistically significant elevated or decreased RRs were found for any disease categories.

Ten or more years after treatment, however, the RR of mortality from circulatory disease was elevated and was due to a statistically significant elevated risk of CHD (RR = 1.24; 95% CI, 1.04–1.47). An analysis of a subset of deaths from acute myocardial infarction (ICD-8 410) showed a statistically significant elevated RR of 1.44 (95% CI, 1.10–1.86) for this cause ≥10 years after RT (data not shown). The RR of CHD did not show a statistically significant trend by age at treatment. The RR was 1.33, 1.37, and 1.10 for those treated at 35–44, 45–54, and ≥55 years of age, respectively, compared with those treated at ≤35 years. The RR of CVD ≥10 years after treatment was elevated, but the difference was not statistically significant (Table 2). The RRs were elevated for gastric/duodenal ulcers, infections, and diseases of the endocrine and genitourinary systems and was decreased for respiratory disease, but none were statistically significant.

Table 3 presents the RRs of CHD and other heart disease by cardiac-dose quartile among patients who lived ≥10 years after treatment. The average total cardiac dose, which is the sum of the volume-weighted doses from all treatments received, ranged from 1.6 Gy (mean in the lowest quartile) to 3.9 Gy (mean in the highest quartile), and the mean in-field doses (doses to the 5% of the heart presumed to be in the field) ranged from 7.6 to 18.4 Gy. Quartile-specific estimates of RR of CHD increased with an increasing level of cardiac dose (p for trend = 0.01), and the RRs for the greatest two dose categories were significantly greater than unity (RR = 1.54 and 1.51, respectively).

No clear patterns were observed for RRs of other cardiac disease in relation to the cardiac doses. Most of the 118 deaths from other cardiac diseases reported on the death certificates were "symptomatic" or ill-defined (n = 59), followed by hypertensive disease (n = 35), cardiomyopathy or myocardial insufficiency (n = 22), and endocardial dis-

Table 1. Relative *risks of coronary heart disease and cerebrovascular disease by patient characteristics

	Effect on baseline risk						
	Coronary heart disease		Cerebrovascular disease		Patient distribution (%)		
Patient characteristic	RR*	Deaths (*n*)	RR*	Deaths (*n*)	Irradiated	Nonirradiated	$p^{\dagger}$
Age at treatment (y)							
<35	1.00	(121)	1.00	(29)	14.6	23.5	<0.001
35–44	3.11‡	(292)	1.94‡	(60)	26.4	29.5	
45–54	7.32‡	(359)	3.85‡	(65)	29.5	26.7	
≥55	17.53‡	(325)	17.44	(97)	29.5	20.3	
Calendar year of treatment							
<1940	5.01‡	(240)	5.78‡	(47)	12.2	28.7	<0.001
1940–1944	3.14‡	(250)	4.63‡	(66)	21.7	24.7	
1945–1949	1.99‡	(236)	2.84‡	(57)	16.8	27.1	
1950–1959	1.46‡	(326)	1.65‡	(70)	40.9	19.5	
≥1960	1.00	(45)	1.00	(11)	8.4	0	
Gender							
Female	1.00	(214)	1.00	(79)	19.8	23.5	0.006
Male	1.56‡	(883)	0.83	(172)	80.2	76.5	
Race							
Black	1.00	(18)	1.00	(79)	3.2	0.5	<0.001
White	1.11	(1,061)	1.05	(172)	94.0	98.5	
Marital status§							
Married	1.00	(863)	1.00	(196)	77.5	79.0	<0.001
Never married	0.93	(105)	0.81	(23)	9.3	12.6	
Divorced/widowed	1.27‡	(113)	1.25	(27)	10.2	7.85	
Cigarette habits§							
Never smoked	1.00	(294)	1.00	(74)	23.8	26.8	0.003
≤1 pack/d	1.21‡	(430)	1.34	(94)	39.6	39.0	
>1 pack/d	1.24‡	(165)	1.08	(26)	17.5	12.4	
Unknown amount	0.89	(23)	1.11	(6)	1.8	1.9	
Unknown status	—	(185)	—	(51)	17.3	19.8	
Alcohol habits§							
Never drank	1.00	(393)	1.00	(91)	33.1	34.5	0.729
≤5 drinks/wk	0.90	(248)	1.09	(61)	23.3	20.4	
6–15 drinks/wk	1.18	(78)	0.71	(15)	8.1	6.6	
>15 drinks/wk	1.12	(91)	0.94	(19)	9.7	7.7	
Unknown amount	0.96	(75)	0.53	(12)	6.1	8.0	
Unknown status	—	(212)	—	(53)	19.7	22.8	

Abbreviation: RR = relative risk.
* RR adjusted for age at treatment, calendar year at treatment, gender, and smoking status (excluding factor of interest tested).
† Test for independence.
‡ 95% Confidence interval excluded 1.0.
§ At time of treatment at University of Chicago; missing data coded as a separate category, estimates not shown.

ease (n = 2). No statistically significant differences were observed in the frequencies of these specific disease categories between the irradiated and nonirradiated groups.

The proxy carotid doses were less than one-tenth of the volume-weighted cardiac doses, with mean quartile doses of 0.10–0.24 Gy. The RR of CVD showed no statistically significant trend in relation to the proxy carotid doses. The quartile-specific RRs for the irradiated patients were 1.36 (lowest dose category), 0.99, 0.98, and 0.82 (highest dose category).

The increase in the RR of CHD for smokers, adjusted for RT, was statistically significant (RR = 1.40; 95 CI, 1.14–1.71). The increase in the RR of CHD for RT, adjusted for smoking, was also statistically significant (RR = 1.20; 95% CI, 1.01–1.43). These results indicated that RT and smoking independently increased the CHD risk. When stratified by smoking status (Table 4), the RR of CHD associated with RT was not increased among nonsmokers but was significantly increased among smokers (RR = 1.40; 95% CI, 1.14–1.71), suggesting an interaction on the multiplicative scale between RT and smoking as CHD risk factors. The test for interaction, however, was of only borderline statistical significance (p = 0.063).

Table 2. Mortality from all causes and selected causes other than cancer: Observed and expected number of deaths by radiotherapy status and relative risk associated with radiotherapy

	Radiotherapy				Years after treatment			
	Yes (n = 1859; PY = 41,779)		No (n = 1860; PY = 51,200)		<10		≥10	
Cause of death (ICD-8 code)	Observed	O/E	Observed	O/E	RR*	95% CI	RR*	95% CI
All causes (001–998)†	1543	1.19‡	1493	0.92	0.88	0.69–1.13	1.14	1.04–1.25
Circulatory diseases (390–458)	806	1.10‡	815	0.87‡	0.83	0.6–1.15	1.10	1.0–1.24
Coronary heart disease (410–414)	551	1.19‡	546	0.96	1.02	0.58–1.81	1.24	1.04–1.47
Cerebrovascular disease (430–438)	127	1.04	124	0.76‡	1.48	0.54–4.05	1.08	0.79–1.49
Respiratory diseases (460–519)	86	0.90	105	0.88	0.98	0.31–3.15	0.78	0.54–1.12
Digestive diseases (520–577)	82	1.70‡	81	1.37‡	0.97	0.48–1.96	1.09	0.72–1.65
Gastric and duodenal ulcers (531–533)	33	3.96‡	33	3.20‡	0.93	0.38–2.26	1.65	0.85–3.23
Infections (001–139)	16	0.89	15	0.62	0.66	0.14–3.09	1.67	0.64–4.37
Endocrine diseases (240–279)	23	0.89	12	0.36	1.0	0.06–16.63	1.32	0.54–3.23
Genitourinary diseases (580–629)	36	1.40	27	0.79	0.90	0.19–4.21	1.63	0.86–3.09

Abbreviations: PY = person-years; O/E = observed deaths/expected number of deaths ratio; RR = relative risk; CI = confidence interval.

* RR for irradiated vs. nonirradiated, adjusted for age and calendar year at treatment, gender, and amount of cigarettes smoked using Cox model; for coronary heart disease, additionally adjusted for marital status and alcohol consumption.

† Causes of death unknown for 11 irradiated and 15 nonirradiated patients.

‡ $p < 0.05$.

DISCUSSION

We found a statistically significant elevated risk of CHD in patients who underwent cardiac RT during treatment of PUD. We estimated that 5% of the cardiac volume (apex) was directly in the radiation field and received mean cumulative absorbed doses of 7.6–18.4 Gy (in-field dose). The remaining 95% of the cardiac volume outside the field received scattered radiation, and, thus, the heart as a whole received volume-weighted doses of 1.6–3.9 Gy. We found the CHD risk to increase significantly with an increasing level of cardiac dose, and the relative risk of CHD was significantly elevated among subjects in the two highest dose quartiles. The excess CHD risk occurred ≥10 years after radiation exposure and was not explained by the confounding effects of cigarette smoking, alcohol consumption, marital status, or other demographic variables. Although it is still possible that the observed excess CHD risk may be explained by residual confounding of other factors, the statistically significant dose-related trend for CHD risk strongly suggests the causal effect of RT. It has been suggested that PUD patients who were selected for RT may have had serious heart conditions unfavorable for surgical

Table 3. Relative risk of coronary and other heart disease: 10-year survivors

			Coronary heart disease		Other heart disease	
Average total cardiac dose* (Gy)	Mean in-field dose† (Gy)	Patients (n)	Deaths (n)	RR‡ (95% CI)	Deaths (n)	RR‡ (95% CI)
0	0	1568	484	1.00 (reference)	60	1.00
0.1–1.9 (1.6)	7.6	368	94	1.00 (0.76–1.33)	15	1.48 (0.67, 3.30)
2.0–2.5 (2.3)	10.6	384	97	1.23 (0.94–1.61)	11	0.46 (0.18, 1.15)
2.6–3.0 (2.8)	12.9	341	114	1.54 (1.15–2.06)	14	0.70 (0.30, 1.61)
3.1–7.6 (3.9)	18.4	382	121	1.51 (1.15–1.99)	18	1.68 (0.77, 3.65)
Trend p				0.01		NS

Abbreviations as in Table 2.

Data in parentheses are mean values, unless otherwise noted.

* Average dose to entire heart.

† Dose to portion (assumed 5%) of heart in beam; dose range was 0.86–9.1 Gy (lowest quartile), 9.2–11.7 Gy, 12.0–13.9 Gy, and 14.4–35.6 Gy (highest quartile).

‡ RR adjusted for age at treatment, calendar year at treatment, gender, number of cigarettes smoked, marital status, and alcohol consumption.

Table 4. Relative risk of coronary heart disease according to smoking and radiotherapy status: 10-year survivors*

	No RT		RT	
Smoking	RR†	Deaths (*n*)	RR†	Deaths (*n*)
No	1.00	150‡	0.94	94
Yes	1.19	244	1.58§	270

Abbreviations: RT = radiotherapy; other abbreviations as in Table 2.

RR for smoking adjusted for radiotherapy 1.40 (95% CI 1.14–1.71); RR for radiotherapy adjusted for smoking 1.20 (95% CI 1.01–1.43); interaction $p = 0.063$.

* Total of 632 patients with unknown smoking status excluded from analysis.

† RR adjusted for age and calendar year at treatment, gender, marital status, and alcohol use.

‡ Reference group.

§ Statistically significant.

treatment (26), and that such selection may have led to a spuriously increased risk of CHD in the irradiated patients. However, if such selection had occurred, the excess risk likely would have been observed sooner, within 10 years after treatment, rather than later, and it was not.

Myocardial infarction has been known to occur as a medical sequela of high-dose mediastinal RT, especially after megavoltage mantle fields and total lymphoid RT used for treatment of Hodgkin's lymphoma in early years (2, 3, 33). RT used for Hodgkin's lymphoma before 1965–1970 yielded a total mediastinal dose of 40–44 Gy. New techniques have reduced the irradiated dose volume; the therapy for Hodgkin's lymphoma currently in use typically yields about 30–35 Gy for adults and 15–25 Gy for children (34). The published study results are inconclusive regarding the cardiac risk from modern, lower dose RT. In a multiinstitutional study of Hodgkin's lymphoma patients treated with RT and chemotherapy, the relative risk of myocardial infarction among patients diagnosed after 1966 was not significantly lower than that among patients diagnosed before 1966, when orthovoltage RT was commonly used (2). A lack of a statistically significant elevated risk of myocardial infarction at a mediastinal dose of <30 Gy has been reported from the Stanford study of Hodgkin's lymphoma patients, but these data were based on few cases (3).

An increased risk of cardiovascular disease has also been attributed to an old series of postmastectomy RT that typically delivered a breast tumor dose of 40–50 Gy, irradiating a large volume of the heart (4–7). More recent RT used for early-stage breast cancer in conjunction with breast-conserving surgery typically exposed 0–5% of the left ventricle to about 25 Gy (14, 35, 36). The results are also mixed regarding the cardiac effects from several studies of patients treated with modern RT used with breast-conserving surgery (10–14). Therefore, the safety of modern, lower dose RT for Hodgkin's lymphoma and breast cancer remains uncertain.

Our study of PUD patients demonstrated a dose–response relationship for CHD in the range of irradiated cardiac dose and volume less than that from RT used for Hodgkin's lymphoma or breast cancer. We found a statistically significant elevated risk of CHD among PUD patients who were in the third dose category (Table 3). The estimated mean cumulative dose for these patients was 12.9 Gy to 5% of the cardiac volume and 2.8 Gy to the entire heart volume (volume-weighted average). However, different tissues of the heart may differ in sensitivity to radiation damage. In the PUD patients, the apex of the heart was exposed to the high in-field dose, but, in patients irradiated in conjunction with breast-conserving surgery, 0–5% of the left ventricle is exposed to high doses (14). Damage to the proximal portion of the main coronary arteries may be especially important for CHD risk (36). In the Stanford study of Hodgkin's lymphoma (3), subcarinal blocking, which reduces the irradiated volume of the heart but does not protect the proximal part of the coronary arteries from RT, was not associated with a decreased risk of myocardial infarction, although it did significantly reduce the risk of mortality from non–myocardial infarction (3).

It is not clear how damage to the small portion of the heart may have contributed to CHD in PUD patients. One may speculate that direct damage from high in-field doses to the ventricular tissue located in the apex may have exacerbated underlying aging-related atherosclerotic changes. Given the demonstrated low-dose radiation effect on heart disease risk among atomic bomb survivors, it is also conceivable that lower dose scattered radiation of the entire heart volume may have contributed to the increased CHD risk among PUD patients. It is, therefore, of special interest that an increased risk of cardiovascular disease has been observed after RT for testicular cancer (37). It was estimated that irradiated testicular cancer patients had a mean cardiac dose of 0.76 Gy, with a mean maximal dose of 3.36 Gy, mostly from scattered radiation. After excluding a small number of patients who had undergone mediastinal RT, the cardiovascular disease risk remained elevated among the patients who largely had received scattered radiation from infradiaphragmatic RT. Our study data did not enable us to distinguish between any effects of in-field doses vs. scattered doses, but it may be relevant to note that the irradiated PUD patients did not have an increased risk of non-CHD heart disease, suggesting that local cardiac damage from the in-beam dose may have been limited.

An important source of uncertainty with the present estimated doses is the assumption that the PUD patients all had 5% of the heart volume in the treatment field. We believe the irradiated portion of the heart was small, because precautions were taken to avoid unnecessary irradiation of the surrounding tissues, using fluoroscopic outlining of the stomach (25), but the irradiated portion could have been >5% or <5%. It is important, however, to recognize that, even if one had assumed this proportion to be 10%, this would have increased the average total cardiac dose only by 24% and the range of the total average dose from 1.6–3.9 Gy to 1.9–4.8 Gy (Table 3), still relatively low. The irra-

diated proportion also varied among patients. The primary source of individual variation in cardiac dose estimates were the stomach doses, which varied markedly by the number of treatments given. In addition, the volume of the heart in the beam would have varied, depending on the individual body size and the location of the heart relative to the stomach and other characteristics. Information on these patient characteristics was not available. However, the failure to consider such individual characteristics is unlikely to have spuriously caused the dose-related increase in CHD risk. Dose estimates that accurately account for individual variations, together with information on the location of specific cardiac pathologic features, would have helped to assess individual doses more accurately and to determine the effects of infield compared with scattered doses on specific types of radiation-induced damage.

To date, the most convincing evidence of elevated heart disease risk from relatively low doses of radiation comes from the Japanese atomic bomb survivor studies, which demonstrated a significant dose–response relation for heart disease and stroke at doses of <4–5 Gy (15, 16). These results were not attributable to confounding by other risk factors, misclassification in causes of death, or other possible biases. Although the mechanisms by which atherogenesis is induced by low-dose radiation remain elusive, recent evidence of the radiation effect on C-reactive protein, interleukin-6, and other inflammatory markers (38, 39) suggests an involvement of clastogenic factors induced by ionizing radiation (40). Inflammatory processes are currently thought to underlie the atherosclerosis responsible for myocardial infarction (41–43).

The relationships of cardiovascular diseases with cigarette smoking, hyperlipidemia, hypertension, obesity, diabetes, and physical activity are well established (44). The contributions of these risk factors, other than of smoking, could not be adequately addressed in our study. The smoking information was somewhat limited in that the intensity of exposure, such as the number of cigarettes smoked daily, was unknown for about 25–30% of the patients. It seems unlikely, however, that this caused a statistically significant bias because the smoking behavior appeared similar among the irradiated and nonirradiated patients. An association between *Helicobacter pylori* infection and CHD has also been suggested but remains controversial in the literature (45–47). *H. pylori* is also one of the etiologic agents involved in PUD (48). No information on *H. pylori* infection status was recorded in the medical records of the patients in our study during the era in which they were treated. *H. pylori* would not confound the relationship between RT and CHD, because the irradiated and nonirradiated patients were equally likely to be have been affected by *H. pylori* infection. However, additional studies of possible interactions between radiation and this and other microbial infections will be of interest in view of the possible long-term impairment of T-cell mediated immunity by radiation exposure (49) and the link between infections and myocardial infarction.

In previous studies of irradiated Hodgkin's lymphoma patients (2), no differences were found in risk of myocardial infarction by history of cigarette smoking, hypertension, or diabetes, suggesting no interaction between RT and other risk factors. In another study of irradiated Hodgkin's lymphoma patients (50), the incidence of ischemic heart disease was not greater than expected in the absence of smoking, hypertension, obesity, diabetes, but the expected incidence, which was derived from the general population, including individuals with risk factors, may have been overestimated. We found that RT and smoking independently contribute to CHD risk. The possible interaction between RT and smoking suggested by the present data is uncertain.

Although RT is no longer used for treating PUD, the finding from this study has important public health and clinical implications. The long-term cardiac risk found in this, and other studies, underscores the importance of continuing follow-up of patients treated with modern chest RT for Hodgkin's lymphoma, breast, and other cancers. There has also been a rapid increase in the use of fluoroscopically guided diagnostic and interventional procedures in the past few decades (51, 52). Radiation doses received during these procedures may range from about one to several Gray (53). Diagnostic coronary angiography and vascular interventions are performed in increasing numbers. In the United States, it was estimated that >700,000 percutaneous coronary angioplasties were performed in 1996 (51). That such large populations are exposed at substantial doses is a cause for concern regarding long-term health consequences.

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